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SENSITIVE
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STATE FOR EAP/MLS, EAP/EP, INR, OES/STC, OES/IHA, MED
STATE PASS TO USAID FOR ANE AND GH
DEPARTMENT OF DEFENSE FOR OSD/ISA/AP (STERN)
HHS/OSSI/DSI PASS TO FIC/NIH (RGLASS) AND OGHA
(WSTIEGER/LVALDEZ/DMILLER)
USAID FOR ANE (CJENNINGS, MWARD) AND GH (KYAMASHITA, KHILL)
CDC FOR COGH (SBLOUNT), CCID (SREDD) AND DIV-FLU(COX/MOHEN)
USDA PASS TO APHIS, FAS (OSTA AND OCRA), FSIS
BANGKOK FOR RMO, CDC (MMALISON), USAID (MACARTHUR/MBRADY/CBOWES),
APHIS (NCARDENAS), REO (JWALLER)
BEIJING FOR HHS HEALTH ATTACHE (BROSS)
PHNOM PENH FOR CDC INFLUENZA COORDINATOR(WBRADY)
ROME FOR FAO
VIENTIANE FOR CDC INFLUENZA COORDINATOR (ACORWIN)

E.O. 12958: N/A
TAGS: TBIO AMED EAGR PINR KFLU VM
SUBJECT: CLINICAL TRIALS FOR HUMAN AVIAN INFLUENZA VACCINE BEGIN IN
VIETNAM

REF: 07 Hanoi 890

1.(U) Summary. After several years of development, the Government of Vietnam (GVN) recently initiated a follow-up human clinical trial for a vaccine against infection with the H5N1 strain of highly pathogenic avian influenza (HPAI). The trial is ongoing at one of three national vaccine research and development sites, with trials expected on different HPAI vaccines at the other two sites in 2009. The United States Government (USG) has provided financial and technical assistance to two of the three Vietnamese institutes, enabling them to produce pilot lots of vaccine strains. USG support covers development, manufacturing, and scale up of pandemic-like influenza vaccines, but not the design, participation, nor oversight of the clinical trials. By 2009, Vietnamese producers hope to have the capacity to manufacture millions of doses of HPAI vaccines produced according to international good manufacturing practice (GMP) standards. This progress is consistent with the long-term U.S. goal of independent manufacture by Vietnam of vaccines against seasonal and pandemic influenza. End Summary.

USG Bilateral Support for Vietnamese Human Vaccine Efforts
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¶2. (SBU) In 2006, the Department of Health and Human Services, Office of the Assistant Secretary for Preparedness and Response (ASPR), Biomedical Advanced Research and Development Authority (BARDA), or herein "HHS," awarded a bilateral grant to the Vaccine and Bio-technology Products Company No. 1 (VABIOTECH) in Hanoi. HHS funded VABIOTECH, spun off from the Ministry of Health's National Institute of Hygiene and Epidemiology (NIHE) and now an "independent" company, to develop a cell-based human vaccine to protect against infection with HPAI. [Note: The exact fiscal and legal separation from NIHE is unclear.] This effort complemented Korean loan support of about USD 20 million to build a vaccine manufacturing facility and develop research and production capacity. Dr. Nguyen Tuyet Nga, the epidemiologist and virologist in charge of the trial at VABIOTECH, has publicly credited HHS and the WHO for assistance in project development.

U.S. Funding of WHO Vaccine Assistance in Vietnam

¶3. (U) In 2007, HHS awarded the World Health Organization (WHO) a USD 10 million grant to help fund a global project targeting the development of pandemic influenza vaccines and manufacturing infrastructure in developing countries. Japan provided an additional USD 10 million to this initiative, designed (in line with the Global Vaccine Action Plan of May 2006) to directly include and leverage the pharmaceutical industry from more developed nations in the vaccine research and development process and to fill gaps often seen in the vaccine development pipeline when bringing a product to market in cooperation with developed countries. A first step was the award of preparation grants, including USD 25,000 to Vietnam's Institute of Vaccines and Medical (Biological) Substances (IVAC in Nha Trang), to support technical assistance to improve the quality of applications. After the review of the final applications, WHO

awarded funding to six countries, including a USD 2.7 million IVAC award. The grant covers development, manufacturing, and scale up of pandemic-like influenza vaccines. After several months of bureaucratic and bank delays, IVAC had full access to the funds by the end of April 2008.

VABIOTECH in Hanoi

¶4. (SBU) VABIOTECH developed a candidate pre-pandemic HPAI vaccine derived from the Vietnamese 1194 sub-strain of H5N1 based on longstanding Vietnamese technology using primary monkey kidney cells (PMKC). A WHO evaluation team reviewed this candidate vaccine and preliminary laboratory results in 2006. Although WHO provided informal recommendations, which included concerns of the possibility of contamination of the PMKC by an as-of-yet unknown potential human pathogen, these were never provided officially. VABIOTECH moved ahead and applied to the MOH to begin trials. Following successful tests of the locally produced vaccine on mice in 2007, on March 17, the Department of Science and Training within the Ministry of Health (MOH) approved two Phase I clinical trials, focusing on vaccine safety. In early April, VABIOTECH successfully conducted the first trial on 10 researchers employed directly in the HAPI vaccine production project.

¶5. (SBU) In late April, VABIOTECH initiated a second small-scale Phase I HPAI vaccine trial with 30 student volunteers from the Military Medical Institute (MMI) in the capital. [Note: This was reported in the local press. The use of military recruits for clinical trials presents ethically challenging issues around the volunterism and autonomy of the subjects]. Injections occured on May 17 without incident; subjects will be followed for 56 days. A Phase II trial, expected to begin in June, will include an additional 240 subjects and will focus on antibody production (as an immunogenic surrogate of effectiveness), as well as safety. VABIOTECH's Nga told Michael Perdue, the Deputy Director of the Division of Influenza and Emerging Diseases, ASPR/BARDA/HHS, that Vietnam currently plans to produce a seasonal trivalent vaccine (the industry standard) as well as vaccines specifically targeting H5N1, using reference influenza strains obtained from National Institute for Control of Vaccines and Biologicals (NICVB) in the United

Kingdom. Glaxo Smith Kline and another company refused requests from VABIOTECH to provide reference strains. VABIOTECH has produced over 5,000 doses of seasonal influenza vaccine after receiving certification from NICVB and expects to produce from two to five million doses per year by 2009 at USD 2.00 per dose. Further clinical trials are being planned.

Institute of Vaccines and Medical Biological Substances (IVAC) in Nha Trang
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¶6. (SBU) IVAC is using embryonic chicken eggs (although not ideal, the egg is the international industry workhorse approach to influenza vaccine manufacture) to develop a human vaccine candidate against HPAI also based on a Vietnamese 1194 sub-strain of H5N1.

Though designed to leverage participation from the pharmaceutical industry of more developed middle-income nations, the program failed to succesfully engage international private partners, bascially due to the lack of sufficient mutual, mostly financial, interest. IVAC has just begun construction of a new purpose built egg-grown vaccine production facility (including the supporting chicken farm), which it expects to be complete in early 2009 and which could produce up to 3 million doses of GMP qualified vaccine. Once it completes the facility, IVAC plans to conduct clinical trials in human subjects. IVAC, which recently produced a pilot run of over 5,500 doses of a human vaccine against HPAI named Fluvac, claimed to have had success during just completed animal testing. IVAC projects that it will be able to produce between 500,000 and 3 million doses of Fluvac vaccine at its new facility each year.

Institute Pasteur in Ho Chi Minh City

¶7. (SBU) Starting work in 2006, the third human vaccine production site relies on a promising continuous mammalian cell line, Vero cells, and uses the same strain as IVAC but obtained from the WHO, an approach also being piloted by several multinational pharmaceutical companies (not only against HPAI but also targeting seasonal influenza). Baxter, the proprietary producer of Vero cells, has received multimillion dollar funding from HHS in 2006 for seasonal and pandemic influenza vaccine development; this funding does not touch Vietnam directly. This WHO-approved approach circumvents problems with egg-based manufacturing (e.g., need for reliable supply of large number of clean eggs, and human allergy to egg produced products) but currently the Vero cell process is slower and lower yields limit large-scale production. HCMC Pasteur, one of four regional GVN public health and research centers, receives funding from the Ministry of Science and Technology for the research and development of Paviflu. For this work, HCMC Pasteur receives technical assistance from Dr. Kasiryu of Japan but no direct external funding. Currently in the final stages of the laboratory aspects of development, HCMC Pasteur plans to file for a GVN license at the end of this month.

Challenges

¶8. (U) Each of the Vietnamese human vaccine projects has weaknesses. Developing an effective HPAI vaccine raises technical challenges beyond those faced when producing seasonal influenza, including the deliterious effects of producing vaccine against HPAI on eggs, HPAI-related health risks to laboratory workers, questions about the effectiveness of vaccines produced using these new techniques, and the unproven ability to scale up production during a pandemic. Any vaccine designed using a current H5N1 strain might not offer protection against other strains, which could render these Vietnamese vaccines useless if a pandemic emerges from a strain sufficiently different than H5N1. To better meet these challenges, Mission Vietnam has proposed to IVAC, MOH, ASPR/HHS, and WHO a national conference to review the overall research and development strategy, to consolidate success, and achieve more robust in-country

coordination.

Comment

¶9. (SBU) The GVN has taken a practical approach to human vaccine development, investigating a variety of possible pathways, recruiting multilateral support and funding, focusing on building capacity, and fostering an emerging private pharmaceutical industry for influenza vaccine production. Regardless, and perhaps more importantly, Vietnam's approach to sharing samples of H5N1 (reftel) has clearly facilitated the pace and quality of development. Investment in Vietnam's capacity to produce influenza vaccines, including seasonal vaccines, satisfies a critical long term pandemic preparedness goal -- on this count we are on target. For these reasons, we believe this targeted USG bilateral support and funding of WHO initiatives has met with success. End Comment.

MICHALAK